REMARKS

I. Status of the Claims

Claims 1-31 were filed with the application. Claims 2, 3, 5-8 and 10-31 have been withdrawn from consideration. Thus, claims 1, 4 and 9 are under consideration and have been examined. The claims are rejected under 35 U.S.C. §112, first paragraph (enablement).

II. Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 1, 4 and 9 are rejected for alleged lack of enablement. Claim 1 is considered a linking claim for all canceled claims and arguments presented herein address all of the claims at issue.

The examiner's rejection initially focuses on MPEP §2614.01(a) and *In re Wands*, asserting that the specification does not provide guidance or working examples. It is further alleged that the claims are too broad, and that it would have required undue experimentation for one of skill in the art, at the time of filing, to practice the claimed invention. Applicants respectfully traverse this rejection.

It may be true that inhibiting MEF2 to treat hypertrophy was not well known at the time the present application was filed, but the information provided in the specification, coupled with what was known prior to this invention, would allow one of skill in the art to practice the invention. Recent results (discussed below) further validate the paradigm that underlies the current invention.

Applicants assert that the examiner's current criticism essentially boils down to asking the applicant to not only show that the claimed methods are enabled, and also to provide direct

experimental evidence confirming that each aspect of the claimed methods works. Thus, the rejection appears to rise to the level of requiring a working model, and according to MPEP §2164.02 "an applicant need not have actually reduced the invention to practice prior to filing." It is important to remember that "because only an enabling disclosure is required, applicant need not describe all actual embodiments. The absence of working examples will not by itself render the invention non-enabled. Furthermore, a single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled." MPEP §2164.02.

Turning to the instant specification, Examples 3 and 6 clearly show that MEF2 is activated in response to hypertrophic signals. As stated in these examples, MEF2 would be considered an endpoint in the hypertrophic cascade. Admittedly, while it may be theoretically difficult to treat a disease by targeting a single cellular pathway, MEF2 is a downstream effector of the hypertrophic cascade, a gateway as it were for a variety of cascades and agonists that lead to the development of hypertrophy as signaled by up regulation of MEF2 dependent genes. The activation of MEF2 dependent "fetal" genes is seen in virtually all known forms of pathological cardiac hypertrophy. Thus, inhibiting the role of MEF2 would be expected to benefit patients suffering from hypertrophic response to cardiac insult by a variety of hypertrophic agonists.

Example 6 also goes on to demonstrate the binding of MEF2 to class II HDAC's. As discussed in the attached declaration of Dr. Timothy McKinsey, this binding activity is crucial in the regulation of MEF2 dependent genes, and targeting this interaction has shed further light both on the activity of MEF2 as well as the ability of one to inhibit hypertrophy by inhibiting the activity of MEF2. The inventors have shown that MEF2 associates with class II HDAC's, as demonstrated in the inventor's own U.S. Patent 6,632,628 and U.S. Patent 6,707,686. As shown

therein, as well as in Zhang *et al.* (2002), and McKinsey *et al.* (2002), the MEF2-class II HDAC interaction is a critical, necessary and sufficient interaction for the regulation of hypertrophy. Ablation of this interaction is deleterious to the heart. Both overexpression of class II HDACs and sequestering of HDACs in the nucleus are profoundly anti-hypertrophic, rendering cells not only resistant to hypertrophic stimuli, but actually reversing hypertrophy once it has begun. Knocking out HDACs - in essence eliminating the cellular regulatory molecule for MEF2 - leads to profound and rapid development of hypertrophy (see Zhang *et al.*, 2002).

In addition to the experimental examples, there is sufficient guidance located throughout the rest of the specification to enable one of skill in the art to practice the claimed invention. A wide variety of general and specific methods for inhibiting MEF2 are disclosed and explained. The specification discloses and explains the use of antisense (p. 26), blocking compounds, peptides or antibodies (pp. 28-29), mimetics (p. 29), gene therapy or transfer (pp. 31-51); and furthermore, the specification discloses ways in which these treatments could be delivered or formulated (pp. 65-67). It also discloses methods for screening and identifying molecules and compounds that could be used in the current invention (pp. 58-65). Thus, the descriptive aspects of the specification coupled with the experimental examples more than adequately describes the invention in a way that would enable one of skill in the art to practice the invention as claimed.

Applicants therefore submit that the instant application does indeed enable the current claims, and that the attached references and declaration further support this notion. One of skill in the art would ***not*** have had to pursue exhaustive and "undue" experimentation to practice the invention; the experiments described herein and those reported in later published papers confirm this point. One of skill could clearly appreciate the significant role played by MEF2 in cardiac hypertrophy, and those practicing in the art have successfully extrapolated from the inventor's

work and gone on to validate the concept of inhibiting MEF2-dependent gene transcription using standard approaches that were available at the time of filing and/or were discussed in the application as filed.

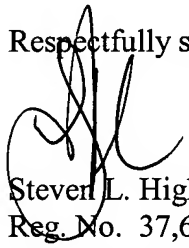
Finally, applicant contends that this rejection goes beyond any reasonable enablement requirement for §112. Applicant refers the examiner to *In re Robins*, 429 F.2d 452 (CCPA 1970) which holds that a "specification which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement ... unless there is reason to doubt the objective truth of the statements therein." The *Robins* court also demands that "Section 112 requires nothing more than objective enablement. How such teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." While more enablement may be required where the art is unpredictable, there is no *per se* rule for a working model. The invention must simply enable one of skill in the art to practice that invention, and there is nothing contained in the current application that goes beyond the capabilities of one of skill in the art (MPEP §2164.01: "[T]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."). As seen in the McKinsey affidavit, one of skill in this specific field would not only accept the inventor's paradigm as accurate, but as ***proved*** subsequent to the filing of present application.

Applicant asserts that, in light of the discussion above and the attached affidavits and references, the rejected claims are in fact enabled by the instant specification. Therefore, it is respectfully requested that the claims be reconsidered and the rejection be withdrawn.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Davis have any questions regarding this response, she is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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SEQUENCE LISTING

<110> OLSON, ERIC N.

<120> METHIODS FOR PREVENTING CARDIAC HPERTROPHY AND HEART FAILURE BY INHIBITION OF MEF2 TRANSCRIPTION

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<141> 2002-01-09

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<150> 60/107,755
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